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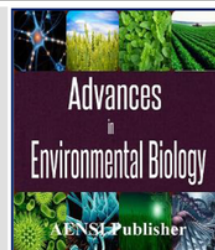


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The Effect of Administration of Leveled Dose Omega-3 Fatty Acid as an Antiinflammatory to the Kidney Histopathological Change of Formalin-Induced White Male Rats (*Rattus norvegicus strain wistar*)

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ABSTRACT

Background: The usage of formalin as food preservative caused negative effect to the body part such as kidney. One of the effects is the damage of kidney's cell that can cause tubule necrosis or well-known as Acute Tubular Necrosis (ATN).

Purpose: Proving the effect of omega-3 to the histopathological image on the kidney of formalin-induced white male rats.

Method: Experimental study with *The Post Test Only Control Group Design*. This experiment used 5 groups and each group consisted of 5 rats (negative control, positive control, fatty acid omega-3 dose 200mg/KgBW/day, 400mg/KgBW/day, 800mg/KgBW/day). After 14-days The kidneys were taken then being analyzed to know the average amount of thyroidisation of tubule.

Result: 1% Tukey test showed that the administration of dose 800mg/KgBW/day yielded a similar result with negative control. The administration of fatty acid omega-3 strongly affected in a negative way, the decrease of the average amount of thyroidisation of kidney's tubule ($R = -0,880$).

Conclusion: It is proven that fatty acid omega-3 has anti inflammatory activity that can prevent the damage of kidney's cell on formalin induced white male rats.

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INTRODUCTION

Acute renal failure or acute kidney injury (AKI) is defined as a suddenly decrease in glomerular filtration rate (within a few hours to several days) that produce metabolic wastes retention such as urea and creatinine, with or without oliguri. Acute renal failure can be caused by several things, one of them is acute tubular necrosis .

Acute tubular necrosis (NTA) is AKI that caused by ischemia or nephrotoxicity in renal tubular epithelium, with tubular epithelial damage and death as the consequences. Prevalence of NTA in America $\pm 1\%$ at admission and $2-5\%$ during care. NTA is the leading cause AKI in hospitalized patients (38 %)

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and intensive care patients (76 %). NTA mortality are 37.1 % and 78.6 % respectively. At 56-60 % of patients, the kidneys may recover completely, while 5-11 % of patients requiring dialysis (1).

NTA can caused by ischemia and nephrotoxins. Ischemia is the most cause of NTA, it can be because of trauma, shock, and sepsis. Trauma can induce hypovolemia and myoglobin release from damaged tissue. Shock and sepsis can induce renal hypoperfusion due to systemic vasodilation and kidney vasoconstriction. Nephrotoxins can cause vasoconstriction or renal tubular injury directly. Nephrotoxins can be derived from endogenous, like myoglobin and exogenous, and can be derived from exogenous, such as drugs and toxins, like formaline.

The use of non-food preservative in many communities are now beginning to be used by food vendors. Non-food preservative that is often used is formalin (2). Formaline is very commonly used in everyday life. In the industrial sector, formalin has many benefits, such as antibacterial or disinfectant, so it is often used for cleaning floors, ship, warehouse, clothing and can also be used as an insect killer (3). The benefits of formaline in industrial often misused for food preservation industry.

According to the IPCS (International Programme on Chemical Safety), the safety levels of formalin in the body is 1 milligram per liter. When formalin into the body over threshold, it can cause disturbance of the organs and systems. The impact can occur in short-term and long-term either through inhalation, direct contact or swallowing (4).

The use of formalin or formaldehyde can effect directly on target organs, because of corrosive to the mucosa, which can cause severe necrosis when ingested. Research shows obtained acute toxic effects on different organ systems, including the digestive system (gastro-intestinal), central nervous system, cardiovascular and hepato-renal system which can lead to vascular collapse, loss of consciousness, and severe metabolic acidosis. In the kidney, oral administration of formaldehyde can cause negative effects such as necrosis of tubular cells, characterized by the tubular dilation, casts, interstitial inflammation, fibrosis, and necrosis (5).

The study of natural ingredients as an anti-inflammatory has been done by many authors. The goal from the use of natural materials is to get the maximum benefit with minimal or no side effects appeared. One of these natural ingredients are omega-3 fatty acid.

Omega-3 is known to have anti-inflammatory effects through various mechanisms, such as changes the composition of cell membranes and decrease the chemotaxis of leukocytes, and other. Anti-inflammatory effects of omega-3 fatty acid may be used as a therapeutic agent (6). Omega-3 is one of the essential fatty acids in the human body because there is no mechanism to form these fatty acids in the human body. Omega-3 can be found in foods such as salmon, mackerel, tuna and plants such as beans. Omega-3 fatty acids are also easily obtained because already on the market as a supplement (7).

Study shows that omega-3 fatty acids can reduce inflammation and is able to reduce the risk of chronic diseases, such as heart disease, cancer and also can improve kidney function. Other studies have shown that intake of omega-3 fatty acids provide the same results for the patients who received therapy arthritis NSAID such as ibuprofen. Administration of omega-3 fatty acids are considered better because there are no side effects were reported compared with the side effects of NSAIDs such as ulcers. So that omega-3 fatty acid is more safety to use (8).

Based on the description above, the writer wanted to do study about the effects of omega-3 fatty acids toward inflammation of the kidneys also the histopathologic changes caused by formaline exposure.

METHODOLOGY

This experimental study used Post Test Only Control Group Design. The sample used is a strain of male Wistar rats (*Rattus norvegicus* Wistar strain). Average of weight is 150-200 grams and average of aged is 2-3 months with a healthy condition characterized by active movement and a clear eyes.

In this study there were 5 treatment groups: one negative control group, one positive group and 3 treatment groups with different dose of omega-3 fatty acids (rats induced by formalin dose of 80 ppm / day plus omega-3 doses of 200mg / kg / day, rats were induced formalin dose of 80 ppm / day and omega-3 400 mg / kg / day, and the rats were induced by formalin dose ppm / day of omega-3 and 800mg / kg / day). Formaline dose determination based on previous research (Yasin, 2010; Mesquita et al, 2011) and has been demonstrated through an exploratory study of the strain Wistar rats (*Rattus norvegicus* Wistar strain) with sample results histopathologic changes.

The independent variable in this study is the omega-3 fatty acid. While the dependent variable in this study is the renal histopathologic change of wistar strain white rats. Formalin induced for 2 weeks with 80 ppm dosage. Omega-3 fatty acid that is used is an oil from a supplement softgel form. Target

observed was tiroidisasi tubular and counted in 5 visual fields using light microscope with 400x magnification.

RESULTS AND DISCUSSION

Based on histopathological observations of kidney rats in group 1 (negative control) and group 2 (positive control), there are significant differences in the average number of tiroidisasi in both groups (Anova and Tukey test sig 0.000). This significantly is due to the group 1 (negative control) that the rats were given only standard feed, whereas in group 2 (positive control) the rats were fed standard as well as induced formalin orally, with the result that kidney damage characterized by the tiroidisasi tubules. This is consistent with previous studies that oral administration of formalin will cause kidney damage such as necrosis and tiroidisasi (4). (table 1)

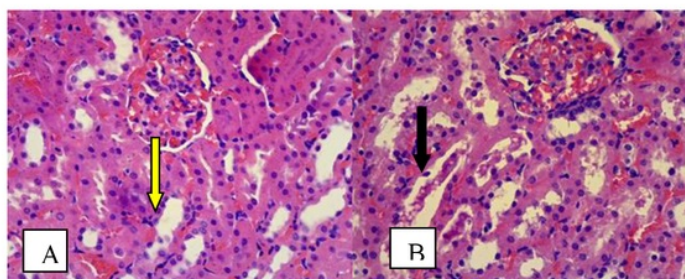


Figure 1: Histopathological change in Kidney rat. A) Negative control group with normal tubules (yellow arrow); B). Positif control group with thyroidisasi tubules (black arrow)

Group	The number of thyroidisasi fo 5 yield					Average
	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	
Group 1	3	0	5	0	3	2.2
Group 2	21	16	17	14	11	15.8
Group 3	14	15	10	14	13	13.2
Group 4	12	7	12	9	10	10
Group 5	2	5	3	3	4	3.4

Table 1: The number of thyroidisasi tubules on each group

The presence of kidney damage caused by toxic, in this case the formaldehyde is converted into formic acid by the enzyme formaldehyde dehydrogenase into formic acid which will then inhibit the activity of cytochrome oxidase in mitochondria, causing barriers to the synthesis of ATP. Furthermore, the cells will undergo hypoxia that can cause cell damage such as necrosis. In addition to toxic due to kidney damage can also be caused by several factors such as stress (4), which is why the group 1 renal tiroidisasi although there are very few.

Results of the analysis group 2 (positive control) and group 3 which has a sig 0.440 means that there is no significant difference between the positive control group with dose group of 200 mg / kg / day, while the analysis of group 2 (positive control) with group 4 and group 5 are has sig 0.008 and 0.000 means there are significant differences between the positive control group with a 400mg dose groups / kg / day and 800mg / kg / day. This is due to the effect of the anti-inflammatory omega-3 fatty acids can protect and improve kidney function. This study is also consistent with previous study by Abdou et al (9) which used omega-3 fatty acid as an anti-inflammatory to protect and improve kidney function.

The role of omega-3 fatty acid as an anti-inflammatory in reducing kidney damage by various mechanisms, such as lowering arachidonic acid as a pro-inflammatory substance in the cell membrane. Then the omega-3 fatty acids can also reduce the activity of phospholipase A, with the result that arachidonic acid metabolism can be decreased. Besides that, omega-3 fatty acids also decrease the activity of the enzyme cyclooxygenase-2. EPA and DHA in omega-3 fatty acids can produce resolvins and protectins

that can compete with LTB₄. All the above mechanism will induce the reduction of eicosanoids (inflammatory mediators)(6).

Based on the analysis Tukey test between group 1 (negative control), groups 3 and 4 which have sig 0,000 and 0,000, which means there are significant differences. While the results in group 1 (negative control) with the group 5 have sig 0.823 which means not significantly different. This is due to the doses of omega-3 fatty acids on the group 5 is a highest dose (800 mg / kg / day), compared to group 3 and group 4 with the result that the average number of tiroidisasi in group 5 is nearest with negative controls group. This is parallel with study by Abdou et al (9) which uses omega-3 fatty acid as an anti-inflammatory that can also protect and improve the kidney function of rats.

Results of the analysis of correlation test (Pearson correlation), which has sig value of -0.880 and 0.000, indicates that the inverse correlation is very strong and there are significant correlation between increasing doses of omega-3 fatty acids with improved renal function and histopathological picture. The higher omega-3 fatty acid doses due to the lower of tiroidisasi tubules. This is parallel with study by Abdou et al (9) which uses omega-3 fatty acids that can provide a more meaningful picture of histopathology at doses of omega-3 fatty acids are higher in reduce the histopathological changes.

Regression analysis has value of R² = 0.774 sig value of 0.000, which means that increasing doses of omega-3 fatty acids were significant influence amounted to 77.4 % of the decrease in the number of tiroidisasi tubules. While the remaining 22.6 % is influenced by other factors such as stress, nutrition and gender (4). But these factors are not examined in this study

A decrease in the average number of tiroidisasi tubules in the group with administration of omega-3 fatty acid which is the highest in this study (group 5 , 800 mg / kg / day) has not equaled the average number of tiroidisasi tubular normal as in group 1 (negative control). This is thought to be caused by doses of omega-3 fatty acid that is used is not high enough so that the optimal dose has not been obtained which can provide a picture of normal rat kidney histopathology. In addition, this research has not been able to look at other factors that could affect the occurrence of renal damage that has not achieved a decrease in the average number of tubular tiroidisasi maximum.

CONCLUSION

Intake of formaldehyde can cause renal histopathology changes that can be seen from the thyroidisasi tubules. The administration of 200mg/kg/day omega-3 did not provide statistically different with 400mg/kg/day positive group from an improvement in the group. 800mg/kg/day give the same results with negative control group.

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